In the United States Court of Federal Claims

No. 15-1066V
(Originally filed: 11/13/2020) [1]
(Re-issued: March 9, 2021)

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KATHY CASTANEDA, on behalf of N.A.C., a minor child,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa-1 to -34 (2018); off-table claim; motion for review; *Althen* test; burden of proof, cytokines, PANS, blood-brain barrier,

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Andrew D. Downing, Phoenix, AZ, for petitioner.

Zoe Wade, Trial Attorney, U.S. Department of Justice, Civil Division, Torts Branch, Washington, DC, with whom were *Ethan P. Davis*, Acting Assistant Attorney General, *C. Salvatore D'Alessio,* Acting Director, *Darryl R. Wishard*, Assistant Director, for Respondent.

OPINION

BRUGGINK, *Judge*.

Pending is petitioner's motion for review of the Special Master's decision of May 18, 2020, denying compensation under the National Childhood Vaccine Injury Act. The matter is fully briefed, and the court finds that oral argument is unnecessary. Because the Special Master was not arbitrary or capricious in determining that petitioner did not meet her burden

[1] This opinion was originally held for fourteen days to afford the parties an opportunity to propose redactions of protected information. They did not propose any redactions. The opinion thus appears in full.

of proving that the vaccines were causally connected to the injury, we deny the motion for review.

BACKGROUND[2]

N.A.C. was born October 9, 2007 and was largely a healthy, happy baby. Ms. Castaneda described N.A.C. as a typical, playful, happy child and provided a video which she said showed him in his typical pre-vaccination state. Shortly before his fifth birthday, on September 26, 2012, N.A.C. received four vaccines: Pentacel, MMR, Hepatitis A, and Prevnar 13. The Washington County Health records from that visit have a box check for "no" to the question "Is child sick today?" Pet.'s Ex. 1 at 1.

Approximately thirty hours later, in Ms. Castaneda's description, N.A.C. began stomping in place, bowing, holding his arms out, and moving his head back and forth. When she asked him to stop, the child said that he was unable to stop and he began telling himself to stop, which his mother described as if he were arguing with his own brain about stopping. *See* Tr. 15-17 (Entitlement hearing, Oct. 4, 2018). Petitioner further testified that N.A.C.'s behavior became aggressive and he began repeatedly banging his head on the floor. Ms. Castaneda also testified that N.A.C. began to later exhibit OCD behavior, which is also recorded in his medical records from doctor visits in 2012 and 2015. For instance, he would straighten all of the labels of items in a grocery aisle or would insist on flushing the toilet three times, crossing the threshold of a room three times, flip lights on and off three times, etc. *Id.* at 18.

According to Ms. Castaneda, N.A.C.'s behavior worsened in the 2-3 days leading up to his birthday on October 9, 2012, 13 days post-vaccination. He had by then a terrible stutter and continued to be violent. That day the Castanedas took N.A.C. to the emergency room at Vidant Medical Center. The complaint for the visit said "mother stated pt has had a change in behavior recently, mother stated recently pt has been having a twitch and will stutter and say stop and then will run a short distance. Pt has had increased crying." Pet.'s Ex. 5 at 2. Paperwork from the visit also states:

[2] The background facts are drawn from the Special Master's opinion and the record below. They are largely not in dispute with a few noted exceptions.

> [N.C.] is a 5 y/o male who presents today with recent behavior problems. Per mother, he has always been an irritable child but has been worse over the past few weeks. He has been fussy, crying more frequently, and misbehaving. He is also walking strangely, taking 1-2 steps then shuffling. Mother states he has also been leaning his head right, then left, then saying "stop." She states he will do this repeatedly. Today is his birthday, and he was behaving normally and eating normally earlier today. Tonight he would not eat dinner and was spitting.

Id.

A CT scan was performed, which came back unremarkable. The doctor agreed that N.A.C. was having symptoms typical of Tourette's Syndrome, but he could not legally diagnose him in the ER. Instead, the Castanedas would need to have N.A.C. examined by a neurologist. According to Ms. Castaneda, when asked if the vaccine could have caused these symptoms, the doctor responded "Yes, there's a possibility." Tr. 26. On October 11, 2012, the Castanedas took N.A.C. to their family physician, Dr. Myung Kil Jeon, who recorded that N.A.C. was having tics and involuntary body movements and referred him to a neurologist. Pet.'s Ex. 13. Ms. Castaneda testified that Dr. Jeon told her that there was a good possibility that the vaccines could have caused the behavior changes. Tr. 31.

On October 15, 2012, Mr. and Ms. Castaneda took N.A.C. to see a children's neurologist at the Children's Hospital of the King's Daughter in Norfolk, VA, at which the Castanedas told the doctor about the tics and violent behaviors mentioned above, such as banging his head against a wall. The Assessment from that visit states, "I explained to the mother that I do not think that these abnormal movements are related to the vaccines. There was no specific data in the medical literature to support such concerns." Pet.'s Ex. 2 at 11. The neurologist, Dr. Miller, could not diagnose N.A.C. with Tourette's that day, but needed to see him over a period of time. Petitioner recalled that Dr. Miller was surprised that N.A.C. manifested so many symptoms all at the same time. Tr. 35.

The Castanedas visited the pediatric neurologist again on November 9, 2012. The records from that visit indicate that N.A.C. had symptoms consistent with Tourette's Syndrome. Pet.'s Ex. 2 at 9. On March 11, 2013, Dr. Miller diagnosed N.A.C. with Tourette's syndrome. That diagnosis was

reiterated in the records of a follow up visit on August 11, 2014. *Id.* at 4. Ms. Castaneda testified that there is no family history of tics or OCD tendencies and that previous to his vaccination N.A.C. had not been diagnosed with OCD, tics, or any other neurological conditions. There is no question that petitioner and her family have suffered a number of hardships in dealing with N.A.C.'s condition thereafter.

On September 25, 2015 Ms. Castaneda, on behalf of her minor child, N.A.C., filed a petition seeking compensation under the National Childhood Vaccine Injury Act. Petitioner has alleged a non-Table claim, wherein petitioner contends that after receiving the Pentacel, MMR, Hepatitis A, and Prevnar 13 vaccinations on September 26, 2007, N.A.C., developed Pediatric Acute-onset Neuropsychiatric Syndrome ("PANS"). On October 4-5, 2018, the Special Master held an entitlement hearing in Washington, DC. *Castaneda v. Sec'y of Health & Human Servs.*, No. 15-1066V, 2020 WL 3833076, *1 (Fed. Cl. Spec. Mstr. June 21, 2018). Medical records, literature, and expert reports were filed before and after that hearing. During the hearing, petitioner presented the expert testimony of Dr. Kiki Chang, and respondent presented that of Dr. Donald Gilbert.

Dr. Chang is a child, adolescent, and adult psychiatrist and a member of the American Academy of Child and Adolescent Psychiatry and the American College of Neuro-Psychopharmacology. *Castaneda*, 2020 WL 3833076 at *8. He was previously on the faculty of the Stanford University Hospital and Children's Hospital. While at Stanford, he formed the university's Pediatric Acute-Onset Neuropsychiatric Syndrome ("PANS") clinic. He organized a meeting in 2013 for researchers and experts to reach consensus on clinical criteria for PANS, which was then achieved. He now runs his own practice, seeing patients of all ages who present with complex psychiatric and neuropsychiatric illnesses. He has seen between 100-200 cases of PANS over the years. He wrote a book on PANS and has over 100 peer-reviewed publications. Dr. Chang was involved in the development of consensus criteria and treatment for children with PANS.

Dr. Chang began by explaining how the PANS diagnosis was developed. In the 1990s, a doctor at the National Institute of Health proposed that a new diagnosis be assigned to children who develop certain neuropsychiatric disorders after having been infected with the streptococcal virus ("strep"). Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus ("PANDAS") was the resulting diagnosis for children who suffer acute onset of obsessive compulsive disorder ("OCD")

with accompanying symptoms like motor tics, behavioral problems, aggressiveness, depression, separation anxiety, and concentration problems after a strep infection. *Castaneda*, 2020 WL 3833076 at *8. What the data eventually showed, however, was that some children would present with an acute onset of these symptoms without a strep infection. For this subset of patients, the PANS diagnosis was proposed and adopted.

For both PANS and PANDAS, Dr. Chang explained that there is a triggering event, either known or unknown, which causes an attack on the basal ganglia in the brain. Researchers and doctors understand the basal ganglia as the affected area because it is where the brain "fine tunes many, if not all, of the brain functions." *Castaneda*, 2020 WL 3833076 at *8. He recited that studies have found basal ganglia abnormalities present with Parkinson's and Tourette's and that studies of the brain have shown the basal ganglia as likewise related to OCD, attention deficit disorders, and tics.

Unlike PANDAS, with which the triggering event is strep, the triggering event is not nearly as clear cut for PANS. A consensus for diagnostic criteria has developed, however. At the 2013 meeting mentioned above, it was agreed that the acuity of onset of PANS symptoms is between 48 and 72 hours, from no symptoms observed to those symptoms necessary for a PANS diagnosis. Dr. Chang further explained that the sudden onset of symptoms differentiated PANS from a more typical diagnoses of OCD and Tourette's, which have more gradual onsets. Further, in PANS diagnoses, the primary diagnostic criterion is OCD behavior or an eating restriction. Secondary to one or both of those symptoms, a PANS sufferer has at least two additional symptoms: anxiety (separation or general), emotional problems, depression, irritability, aggression, oppositional behavior, development regression, hyperactivity, concentration deficits, hand writing changes, memory function problems, sensory motor issues (including motor and vocal tics), and somatic symptoms. *Castaneda*, 2020 WL 3833076 at *9.

Dr. Chang also testified that, with both PANDAS and PANS, there are two possible mechanisms through which the disorders are developed: autoimmune molecular mimicry and a general inflammatory reaction caused by cytokine production. *Castaneda*, 2020 WL 3833076 at *8-*9. With the first, molecular mimicry, the body creates antibodies against a particular antigen, such as strep in the case of PANDAS, which attack tissue in the basal ganglia. This is because the antigen is molecularly similar enough to the brain tissue that the antibody also affects that tissue. It is unknown

precisely how these antibodies cross the blood-brain barrier and cause the inflammation that disrupts the brain.

The second mechanism, the more general inflammatory response to a trigger, is mediated by cytokines. These cells then cross the blood-brain barrier, selectively attack the basal ganglia, and cause PANS symptoms. Dr. Chang opined that, although he was not certain why the cytokine response would target the basal ganglia, this area of the brain is a "ripe area due to where it is located in the vasculature." Tr. 120. The trigger could be an infection, autoimmune condition, or "anything that can really cause an inflammatory state, including a vaccination." *Id.* at 122. It is this cytokine response that Dr. Chang believes caused N.A.C.'s symptoms, which he opined were consistent with a PANS diagnosis. He also added on cross-examination that there is some pending research regarding PANS and a genetic marker, which he was unsure whether N.A.C. possessed. He nevertheless also speculated that N.A.C. likely had a genetic predisposition for PANS. *Id.* at 159.

Dr. Chang discussed four pieces of medical literature during this testimony, which will be discussed in greater detail below. Generally, however, one stood for the proposition that cytokine production was responsible for tic exacerbation in children with tic disorders and Tourette's Syndrome. Parker Athill et al., *Cytokine Correlations in Youth with Tic Disorders*, Journal of Child and Adolescent Psychopharmacology, Vol. 25, No. 1 (2015) ("*Parker Athill*") (filed as Pet.'s Ex. 25). Another study supported the diagnostic criteria of rapid onset of OCD symptoms with PANS. Tanya K. Murphy, et al., *Characterization of the PANS Phenotype*, Journal of Child and Adolescent Psychopharmacology, Vol. 25, No. 1 (2015) (filed as Pet.'s Ex/ 31). The third was a survey of 700 PANS-diagnosed patients in which many reported triggering events involving inflammation, and 300 of which mentioned vaccines as precipitating symptoms. Denise Calaprice, et al., *A Survey of PANS Characteristics and Course*, Journal of Child and Adolescent Psychopharmacology, Vol. 20, No. 20 (2017) ("*Calaprice*") (filed as Pet.'s Ex. 16). The fourth study found an increased incidence of vaccinations in a group of children prior to a diagnosis of anorexia. Douglas Leslie, et al., *Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination in Children and Adolescents: A Pilot Case-Control Study*, Frontiers In Psychiatry (2017) ("*Leslie*") (filed as Pet.'s Ex. 36). Dr. Chang explained that this was relevant to his opinion because anorexia is often a misdiagnosis for food restriction, a relevant criterion for PANS.

Dr. Chang was unsure why N.A.C. had not experienced these symptoms following earlier vaccinations. When asked about autism as possible explanation for N.A.C.'s symptoms, he demurred, explaining that the acuity of onset and multitude of symptoms are inconsistent with autism.

Respondent's expert, Dr. Gilbert, is a practicing physician and professor of pediatrics and neurology. He is board certified in neurology with a special competence in pediatric neurology. After his residency at Johns Hopkins University, he began his current employment at Cincinnati Children's Hospital Medical Center. His practice focuses on movement disorders and neuropsychiatric symptoms associated with basal ganglia and cerebellar dysfunction. He also has a master's degree in statistics and clinical research design. Dr. Gilbert serves on several relevant boards and committees involved with Tourette's Syndrome and pediatric neurology. He testified that he sees approximately six patients per month where PANDAS or PANS was considered by the referring doctor or the child's parent.

Dr. Gilbert's testimony agreed with Dr. Chang about the development of the PANS diagnosis from PANDAS. He agreed that the "thunderclap onset of severe symptoms" unrelated to strep was the distinction that brought about PANS. Tr. 219. Other than the acuity of onset of symptoms, however, he explained that no biological distinction between anorexia or OCD and PANS had been identified. He disagreed, however, that PANDAS was so uniformly thought of as separate from Tourette's or OCD. *Id.* at 217-18. He also stated that, in his opinion, neither autoimmune nor inflammatory mechanisms had yet been identified as the cause of PANS. *Id.* at 219. He further found notable that no immune-modulating response has been found to be helpful in treating PANS. This suggested, to Dr. Gilbert, that much remains to be shown as to whether there is a connection between an immune response and PANS. He found little support for the idea in the *Parker Athill* study cited by Dr. Chang because it found only a marginal increase in one particular cytokine associated with tics of OCD symptoms. *Id.* at 224-27.

Dr. Gilbert testified that it was unlikely that N.A.C.'s symptoms were caused by the vaccines because the 24-hour timeframe was too short for the severe cytokine response necessary for the symptoms suddenly observed. *Castaneda*, 2020 WL 3833076 at *13. He also explained that such an inflammatory process in the brain would cause more generalized symptoms such as seizures and gross motor function disruption. Further, basal ganglia disruption would generally cause other movement disorders, not so neatly

limited to OCD or tics. He thus opined that there is currently a gap in the theories of PANS causation. He also found the rapid onset of symptoms of OCD to be not nearly so atypical and thus not indicative of a triggering event.

In a supplemental report, Dr. Gilbert stated that he found it difficult to determine whether N.A.C. had a motor tic in the video presented of the child prior to vaccination, but he believed that N.A.C. exhibited a misuse of the pronoun "you," which characterizes children on the autism spectrum. Respt.'s Ex. C at 1. He goes on to address other behavioral markers from the video that he believes evinces early autism in N.A.C. He finishes the report by stating that PANS is a weak diagnosis generally because the science behind it is limited and that, in his opinion, N.A.C.'s symptoms are likely caused by autism and not the vaccine.

The Special Master weighed the scientific literature, the expert testimony, and the evidence in N.A.C.'s case and found petitioner did not meet her burden. Specifically, the Special Master found Dr. Chang was unable to demonstrate how vaccinations trigger pathologic levels of cytokine production. While the Special Master noted that cytokine production often accompanies a vaccine, petitioner did not demonstrate what level of production of cytokines would be necessary to cause the inflammatory cascade laid out in petitioner's theory. She noted that Dr. Chang admitted that he did not know what level of cytokine production follows vaccinations and did not know what levels of cytokine production accompanied N.A.C.'s vaccination specifically.

The Special Master was also not persuaded by Dr. Chang's theory that a vaccine-induced cytokine expression would lead to cytokines crossing the blood-brain barrier, as Dr. Chang posited. *Castaneda*, 2020 WL 3833076 at *28. He was unable to explain how they would cross this barrier. Nor was he able to show that such a crossing of the blood-brain barrier by cytokines had occurred in N.A.C.'s case. Petitioner was unable to show why the basal ganglia specifically would be targeted by generalized, vaccine-induced cytokine expression, and petitioner was unable to show that the basal ganglia had been affected in N.A.C.'s case. Showing that N.A.C.'s basal ganglia had been inflamed would have required brain-imaging to be completed close to the time of vaccination, which did not occur. In short, according to the Special Master, petitioner not only failed to demonstrate a generalized theory to explain how vaccination would have resulted in PANS, but also failed to show that any of the necessary steps actually happened in the case of N.A.C.

The Special Master also found significant the fact that none of N.A.C.'s treating physicians connected his vaccines to the onset of his symptoms. *Castaneda*, 2020 WL 3833076 at *29. The Special Master noted that no diagnostic tests of N.A.C. were completed, which might have otherwise lent support to petitioner's theory. The Special Master considered the fact that N.A.C. did not suffer a post-vaccine reaction, such as fever or malaise, as further evidence that petitioner's theory was unavailing.

Finally, the Special Master found that petitioner did not establish a proximate temporal relationship between vaccination and injury. *Castaneda*, 2020 WL 3833076 at *29. While the Special Master confirmed that the rapid onset of symptoms, measured from the start of the symptoms, was consistent with a diagnosis of PANS, she nonetheless noted that the acute onset of symptoms required for a PANS diagnosis relates only to the rapidity of symptom onset and not to the timing between the triggering event and the onset of symptoms. Notably, the Special Master agreed with Dr. Chang that there is no scientific consensus about the timing between a triggering event and the onset of symptoms for PANS. Further, the government's expert witness, Dr. Gilbert, stated his belief that the medical cause proposed by petitioner could not have occurred and resulted in the onset of PANS symptoms in so short a time from the triggering event.

In summary, the Special Master found that the medical theory proposed by petitioner was not adequately supported by expert testimony and was contradicted by more credible expert testimony, that the medical literature used to support petitioner's theory was flawed and ultimately unreliable, and that N.A.C.'s test results, symptoms, and the opinions of treating physicians were not consistent with petitioner's claims. *Castaneda*, 2020 WL 3833076 at *29-*30. Ms. Castaneda now appeals the Special Master's May 18, 2020 decision denying compensation. Petitioner filed a motion for review, pursuant to Vaccine Rule 27 on June 17, 2020. The government responded, and petitioner sought leave to file a reply, which we granted.

DISCUSSION

This court has jurisdiction to review the Special Master's decision in accordance with 42 U.S.C. § 300aa-12. Our review is deferential, only setting aside decisions when they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law . . . ." *Id.* § 300aa-12(e). When the Special Master has considered the relevant evidence and

articulated a rational basis for the decision, reversible error is "extremely difficult to demonstrate." *Hines v. Sec'y Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991). This court does "not reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses–these are all matters within the purview of the fact finder." *Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1249 (Fed. Cir. 2011).

A petitioner may seek compensation for "any illness, disability, injury, or condition" sustained or significantly aggravated by a vaccine. 42 U.S.C. §§ 300aa-11(c)(1), -13(a)(1)(A). When a petitioner seeks compensation for an injury caused by a vaccine other than those injuries listed on the Vaccine Injury Table, an off-table injury, petitioner must prove causation in fact. *Althen*, 418 F.3d 1274, 1278 (Fed. Cir. 2005) (citing 42 U.S.C. § 300aa-13(a)(1)(A)). Petitioner must show that the vaccination caused the injury by proving three elements by a preponderance of the evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* These three elements are referred to, respectively, as *Althen* prongs I, II, and III.

A different showing corresponds to each of the elements, but the same evidence may be used to prove more than one element. First, petitioner must provide a reputable medical theory that demonstrates that the vaccine can cause the alleged injury. A petitioner is not required to submit medical literature, propose a generally accepted theory, or demonstrate proof of scientific certainty. *See Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378 (Fed. Cir. 2009). Yet, petitioner cannot prevail merely on "a 'plausible' or 'possible' causal link between the vaccination and the injury; he must prove his case by a preponderance of the evidence." *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352,1356 (Fed. Cir. 2013) (citing *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1332 (Fed. Cir. 2010)). "[A] mere showing of a proximate temporal relationship between vaccination and injury" is insufficient to prove actual causation. *Althen*, 418 F.3d at 1278.

To demonstrate a logical sequence of cause and effect, petitioner may use reputable medical or scientific evidence, including medical records. *See Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (citations omitted). Additionally, the treating physician's opinion

is entitled to weight, particularly because it was created contemporaneously. *Id.* Finally, petitioner must establish that there is a "medically-acceptable" timeframe between the vaccination and alleged injury that is consistent with the theory of how the vaccine could cause the injury. *De Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

I. Medical Theory of Causation

We begin where the Special Master did—petitioner established that N.A.C. had PANS. *Castaneda*, 2020 WL 3833076 at *22. This finding makes irrelevant much of Dr. Gilbert's opinions regarding the onset of symptoms, the trustworthiness of PANS as a diagnosis, and what caused the symptoms suffered. It does not matter whether N.A.C. exhibited signs of being on the autism spectrum prior to the vaccinations because that does not preclude the diagnosis reached by Dr. Chang, which was ultimately adopted by the Special Master. What remains then is whether petitioner's theory meets muster under the Vaccine Act. Is it a reliable medical theory, with evidence of cause and effect in N.A.C.'s case, and within a medically-acceptable time frame?

The Special Master answered each of those questions in the negative. She synthesized Dr. Chang's testimony and expert report into a four-step theory of causation: 1) the vaccines caused a general (immune) inflammatory response via the production of cytokines; 2) those cytokines increased the blood brain barrier's permeability and did cross the barrier; 3) once across the barrier, the cytokines targeted the basal ganglia; and 4) caused the symptoms of PANS. The parties largely follow that rubric in their briefing on review, but we note that the discussion of steps three and four were combined.

A. Vaccination Promotes the Production of Cytokines

The Special Master found unpersuasive the first pillar on which the petitioner's theory is built, namely that the vaccines could have caused the production of cytokines necessary to trigger the response posited by Dr. Chang. It was not the question of whether vaccines can and do produce an inflammatory reaction, including the production of cytokines, that was troubling for the Special Master. Rather, she found that petitioner neither established, nor attempted to establish, the level necessary to cause the effects posited by Dr. Chang nor what N.A.C.'s cytokine levels in fact were shortly after the vaccine.

The Special Master accepted as generally recognized that vaccines stimulate cytokine production. She cited, however, five vaccine decisions in which "general cytokine-based theories of causation [were] not persuasive." *Castaneda*, 2020 WL 3833076 at *23 (citing *Zumwalt v. Sec'y of Health & Human Servs*, No. 16-994V, 2019 WL 1953739 (Fed. Cl. Spec. Mstr. Mar. 21, 2019); *Namdar v. Sec'y of HHS*, No. 15-1173V, 2019 WL 1160341 (Fed. Cl. Spec. Mstr. Feb. 8, 2019); *McCabe v. Sec'y of HHS*, No. 13-570V, 2018 WL 3029175 (Fed. Cl. Spec. Mstr. May 17, 2018); *Dean v. Sec'y of HHS*, No. 13-808V, 2017 WL 2926605 (Fed. Cl. Spec. Mstr. June 9, 2017)). The Special Master also highlighted Dr. Chang's inability to provide a substantive answer when asked what level of cytokine production is usually observed after vaccination. Without evidence of either the actual reaction or what is expected to normally occur after vaccination, the Special Master found the first step in the Chang theory insufficient.

On review, petitioner argues that her burden of persuasion was not so high. She urges that requiring such evidence—what level of cytokine production would be pathologic—far overshoots the gatekeeping role of the Special Master. Petitioner urges that requiring evidence of a "dose response" is far ahead of the science in this area and is therefore impossible to prove, akin to proving the theory to a level of certainty, which is not required under the act. We agree in part, but nevertheless affirm the Special Master's conclusion.

The Special Master was correct that no evidence was provided regarding the level of cytokine production expected after a vaccine nor what would be necessary to produce the effects posited by Dr. Chang. Whether the Vaccine Act's preponderant standard requires such precision in all cases where a cytokine-mediated theory is offered is a different question. Although we need not reach the question, we note that each case is to be decided on its own facts. The precise combination of clinical, medical literature, and expert opinion evidence varies from case to case. To cite a number of instances, even five, in which cytokine-based theories were found insufficient is of no note. The evidence was not uniform in each of those cases nor does it match what was presented here. The question is whether Ms. Castaneda's evidence, namely Dr. Chang's opinion, is persuasive.

Dr. Chang started with the consensus regarding the criteria necessary to diagnose PANS. PANS and PANDAS are distinct from syndromes causing similar symptoms, like Tourette's, because of the acuity of onset,

which the record bears out here. He also explained that the consensus is that there is a triggering event, known or unknown, prior to the sudden onset of symptoms. Through that lens, he examined N.A.C.'s records and finds only the vaccinations as a likely trigger. He then turned to an explanation of how this could have occurred.

Dr. Chang explained that there are two likely biological pathways for a trigger that can cause PANS. As the Special Master recognized, both experts agreed that the symptoms are likely caused by basal ganglia disfunction based on brain imaging studies of that region and the understanding that it is the fine-tuner of the brains outputs. The first pathway posited by petitioner's expert was an autoimmune reaction resulting in an antibody that would be predisposed to selectively attack the basal ganglia due to molecular similarity between that tissue and the antigen, which he called "molecular mimicry." This mechanism, he testified, was unlikely to be involved here because of the rapid onset of symptoms after the vaccines.

The rapidity of the onset after vaccination suggested, to Dr. Chang, that a much faster biological mechanism must have been involved: an autoinflammatory response. This response would produce cytokines, which crossed into the brain, and caused an inflammatory reaction in the basal ganglia, according to Dr. Chang. If each of those steps could have been established with some evidence of reliable support either in the record or the medical literature, a different result would be likely. The Special Master found that was not the case, however.

B. Cytokines Increase the Permeability of the Blood-Brain Barrier

Next, the Special Master found unavailing Dr. Chang's testimony that cytokines can lead to increased permeability of the blood-brain barrier. He was asked on direct whether a particular cytokine, tumor necrosis factor alpha ("TNFa"), is "expressed after vaccination." Tr. 123. Dr. Chang answered in the affirmative. He was then asked whether the same proinflammatory cytokines can "cause the blood-brain barrier to become more permeable." Tr. 124. He said that they can. The Special Master found this insufficient. She noted that there was no further discussion on the point during the hearing nor any studies or other evidence presented. Without a more detailed explanation of how or why cytokines pass through the barrier, the petitioner could not show with any likelihood that this would happen, according to the Special Master.

She further credited Dr. Gilbert's testimony that, before the barrier could be transgressed, the very tight cellular junctions of that structure would have to be loosened. Dr. Gilbert found it implausible that this process, along with the rest of Dr. Chang's steps, could occur in a period as short as 24 hours. Tr. 228. Lastly, the Special Master cited a similar case in which the TNFa cytokine had been posited as the brain invader: *McGuire v. Secretary of Health and Human Services*. In *McGuire*, a different Special Master ruled against the petitioner's claim that a vaccine caused her to suffer chronic headaches because, *inter alia*, the pharmacologist who testified regarding TNFa crossing the blood-brain barrier did not explain how this occurred. No. 10-609V, 2015 WL 6150598 (Fed. Cl. Spec. Mstr. Sept. 18, 2015) (also of critical importance was the testimony of a neurologist who opined that TNFa does not easily cross the barrier).

We find two errors in the Special Master's holding on this step, but they are ultimately harmless. As pointed out in petitioner's memorandum on review, the Special Master was wrong when she stated that there was "no literature filed in support of the proposition," *Castaneda*, 2020 WL 3833076 at *24. Dr. Gilbert's own work, the *Martino* article, states that "an increase in TNFa would increase the permeability of the blood-brain barrier." *Martino* at 10 (Pet.'s Ex. 44). In fact, Dr. Gilbert and colleagues go on to state that such changes "may lead to an enhanced autoimmue response and even greater dopamine release in the basal ganglia which in turn contribute to the clinical symptoms of [Tourette's] and related disorders," which parallels much of Dr. Chang's opinion.[3] *Id.* The second error was faulting the theory due to a lack of explanation of how cytokines might cross the barrier, as in *McGuire*. Here, Dr. Chang testified, and Dr. Gilbert et al. wrote that the TNFa cytokine does in fact increase the permeability of the blood brain barrier. Further explication of precisely how this is accomplished is not required. *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994) ("to require proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine program").

Ultimately, we agree with Special Master on the point regarding this step, however, because Dr. Chang did not explain why this would happen in such a short period of time. He was neither asked nor otherwise opined on the matter. The Special Master was within her rights to credit the testimony

[3] We note, however, in the *Martino* article, the statement quoted above was in reference to a process kicked off by an immune response to a strep infection rather than a vaccine.

of Dr. Gilbert on the point, who discredited the plausibility of that occurring in the time allotted in the circumstances of petitioner's injury. Here we find this missing link decisive.

C. The Cytokines Target the Basal Ganglia and Cause PANS

The final two steps of Dr. Chang's theory were considered together. The Special Master found insufficient evidence "that rapid cytokine cascade and generalized inflammatory response to vaccinations is a likely mechanism by which targeted basal ganglia dysfunction can result." *Castaneda*, 2020 WL 3833076 at *25. Although she noted that a general link between inflammation and pediatric psychiatric disorders had been observed in medical literature, she found that petitioner had not shown that this sort of generalized reaction to a vaccine would result in the "targeted dysfunction observed in disorders of the basal ganglia." *Id.* She further found unanswered the question of why this inflammatory process would only target the brain regions necessary to cause the symptoms experienced by N.A.C. She agreed with Dr. Gilbert that, when an inflammatory reaction targets the brain (an encephalitis), the symptoms are more generalized, such as seizures, which indicates a wider reaction across the brain. *See* Tr. 366.

Dealing with the study cited by petitioner on this point, the Special Master found that the relationship found in the Parker-Athill article between TNFa and symptom expression in individuals with tic disorders, like Tourette's, was based on too small a sample to extrapolate a solid correlation from the findings. She also correctly noted that this study, even if fully credited, only showed a relationship between tic exacerbation and the cytokine level, not that the cytokine caused the symptom. Likewise, a survey of PANS patients who reported flare-ups following flu vaccinations was found unpersuasive because it relied on self-reported data and was not specific regarding the dose, the temporal interval between vaccine and symptom, nor whether the symptoms were chronic, i.e., unlikely to have been caused by the recent flu vaccine. *See Calaprice* at 1.

The temporal relationship between receiving a vaccine and the onset of neuropsychiatric disorders reported in the *Leslie* study was criticized by the Special Master and Dr. Gilbert as the product of insufficiently qualified authors and because the study found correlation between presumably non-vaccine caused injuries, such as broken bones, and the vaccines. Quoting Dr. Gilbert, the Special Master thus dismissed the findings regarding tics and OCD as "statistical noise." *Castaneda*, 2020 WL 3833076 at * 26 (quoting Tr. 247).

Lastly, the article that Dr. Gilbert co-authored, *Martino*, which petitioner cited as support for her theory generally, was discounted because the hypothesis that tics and obsessive behaviors might be "directly or indirectly precipitated by cytokines" was merely that, a hypothesis. Pet.'s Ex. 44 at 9. Because the study also noted that "clear evidence of cytokine-induced neural dysfunction in [Tourete's Syndrom] is lacking and should be further addressed in future studies," the Special Master found that, by itself, the study was insufficient to push petitioner past her evidentiary burden. In sum, the Special Master found that the role of cytokines in these disorders was being investigated and that the evidence available was short of a "sound and reliable theory." *Castaneda*, 2020 WL 3833076 at *26. The Special Master thus found that petitioner had failed to establish the first prong of *Althen*.

To support Dr. Chang's causal theory, petitioner cites a survey by Dr. Calaprice and a study by Dr. Leckman. But these articles were considered in great detail by the Special Master and found to be flawed, unpersuasive, and ultimately not supportive of petitioner's case. Even petitioner noted that *Leckman* did not provide more than a temporal link between vaccines and symptoms: "preliminary epidemiologic evidence that the onset of some pediatric-onset neuropsychiatric disorders, including AN, OCD, anxiety disorders, and tic disorders, may be temporally related to prior vaccinations." MFR at 17, 23 (quoting Pet.'s Ex. 36 at 6). This is well short of providing a reliable theory or even filling in the blanks left in Dr. Chang's theory. *Calaprice* provided only a correlation in blood serum levels of TNFa and symptoms. Although relevant in a very general sense, this provides no evidence that cytokines have crossed the blood brain barrier and are selectively attacking the basal ganglia. Likewise, the Special Master was not irrational in her weighing of the probative value of the *Parker Athill* article.

We agree with the Special Master that Dr. Chang's opinion and the literature cited by petitioner are short of supporting the final two steps in Dr. Chang's theory. The only bridge offered by Dr. Chang was a genetic susceptibility. That possibility was purely hypothetical and almost entirely unexplored in his testimony and expert reports. He testified to one yet unpublished study regarding a particular gene expression that might be relevant. That is not reliable evidence and the Special Master did not err in declining to rely on it to bridge any of the gaps in petitioner's theory. We also find no error in the Special Master's reliance on Dr. Gilbert's critique that a generalized inflammatory response caused by invading cytokines in

the brain ought to have caused more generalized symptoms. This cast significant doubt on steps three and four in Dr. Chang's theory. The Special Master was neither arbitrary nor capricious in rejecting them.

II. A Logical Sequence of Cause and Effect

On the question of whether petitioner had established by preponderant evidence that there was a logical chain of cause and effect between the vaccine and PANS, the Special Master began that, since she found no medically reliable theory of caution, no cause and effect could be found either. But even assuming a theory was posited and accepted for how the vaccines caused PANS, the Special Master found insufficient proof that it did in fact happen in this case. She cited the lack of a similar or same diagnosis by the child's treating physicians. Further, the lack of immune testing and brain imaging of N.A.C. was problematic for the petitioner, in the Special Master's view because, as Dr. Chang admitted, he could not know for a fact whether there was inflammation in the child's basal ganglia or whether there were elevated cytokine levels that might have caused it. Finally, there was no evidence in the medical records presented that N.A.C. experienced any reaction to the vaccine. The Special Master noted the absence of a fever or any malaise, which she would have expected to see had N.A.C. experienced a negative reaction to the vaccines he received. *Castaneda*, 2020 WL 3833076 at *29.

Although we agree with petitioner that medical records are not dispositive on the question, and we find that the Special Master's own opinion regarding the absence of an immune response after vaccination is irrelevant, we need not reach the question of whether there was error that prejudiced petitioner as to this prong of the test. Had petitioner provided a reliable explanation of how the vaccine caused PANS in the time period she posited, the fact that no doctor diagnosed PANS prior to Dr. Chang would be largely immaterial. Also immaterial would have been the lack of a fever experienced by N.A.C. after receiving the vaccine. The Special Master cited no record evidence for why that should be dispositive of the issue. Had the first prong of causation been met, reversal would have been merited for reconsideration of the logical connection between the vaccine and the injury.

III. Proximate Temporal Relationship

Lastly, the Special Master found that Ms. Castaneda had not established a timeframe in which it was "medically acceptable to infer

causation." *Castaneda*, 2020 WL 3833076 at *30. The 30-hour onset of N.A.C.'s symptoms was inconclusive in the Special Master's view because she found Dr. Chang's opinion on the matter unclear and inconclusive. Although we think that the record is clear enough that Dr. Chang's testimony regarding the onset of PANDAS symptoms after strep infection was meant as a contrast to his opinion regarding onset after a vaccine-triggered event, her more general holding that Dr. Chang had not explained why a rapid cytokine response could cause PANS in only a day was rational. Dr. Chang's testimony regarding the acuity of onset, as argued in petitioner's papers, was not directly on point. It went to the issue of why a PANS diagnosis rather than how fast vaccine ought to have caused the onset of those symptoms. The Special Master's view on this point was neither arbitrary nor irrational.

CONCLUSION

Although the Special Master appears to have required more than is required by the Vaccine Act on some of the finer points, we find those errors harmless. The conclusion reached was not contrary to law and not irrational. Accordingly, we deny petitioner's motion for review. The Clerk of Court is directed to enter judgment accordingly.

s/Eric G. Bruggink
ERIC G. BRUGGINK
Senior Judge